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Project Report

Project Title:

Dengue and El Niño/Southern Oscillation Events in Yogyakarta Indonesia: Historical Correlations, Mechanisms, and Recommendations for Control Using Source Reduction

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Table of Contents

Summary

Recent developments of estimates of transmission thresholds for dengue in terms of *Ae. aegypti* pupae per person as a function of temperature and herd immunity, along with a new surveillance method that permits estimating the absolute productivity of each type of container in the environment suggests that it may possible to develop targeted source reduction strategies that control only a limited subset of containers. Early warning systems could enable these targeted approaches to be applied only during times leading up to predicted epidemics,

The funding from this NOAA-OGP was used for the following:

1. Analyze 4 extensive pupal/demographic surveys conducted by the US Navy and Gadjah Mada University in Yogyakarta, Indonesia (1996-1999). This analysis document the various types of breeding containers in the environment, provides in absolute term, the number of *Ae. aegypti* pupae per person associated with each, and how these two variables vary seasonally with rainfall.
2. This analysis has permitted the development of a targeted breeding source reduction/control program that relies on attempting to control only 2-3 of the more than 50 types of containers in the environment. The chief benefit of this strategy is labor savings.

The dengue models developed by Focks *et al.* were parameterized with the analysis results. This permitted using the models to investigate the linkages between weather anomalies associated with ENSO state and dengue dynamics in Java, Indonesia. Three particularly important phenomenon were documented.

   a. Weather anomalies do in fact influence the interannual variability in dengue transmission in this region of the world.
   b. Atmospheric dryness associated with ENSO in this region is not low enough to influence the dynamics of *Ae. aegypti* nor of dengue.
   c. The chief environmental linkage between climate and dengue involve temperature anomalies that influence the speed of viral dissemination in the vector and the length of the gonotrophic cycle.

3. These linkages have permitted the development of a dengue early warning system that predicts epidemic periods 1, 2, and 3 months in the future based on lagged dengue cases and sea surface temperatures.

The results of these NOAA-OGP-funded studies have lead to three developments.

   a. The WHO/UNDP/World Bank (TDR) is evaluating this system in 10 countries in the Americas, Africa, and Southeast Asia.
   b. A private Indonesian foundation is funding a demonstration control project in Yogyakarta beginning in 2003. The project will involve the control strategy and EWS documented herein.
   c. A more sophisticated EWS has been developed with monthly predictions forecasting dengue incidence 1 to 5 months in advance.
   d. A collaboration with the PI with IRI Climate Prediction Center is underway to develop an EWS based on NOAA's ENSO forecasts.

Final Report

This report will cover what was conducted and presented and/or published under the NOAA-OGP funding for FY 99. It will also present subsequent and ongoing activities that were the result of the findings under this grant but conducted with additional funding from other agencies or private sources. Briefly, the NOAA-OGP funding permitted 1) the parameterization of the dengue models in Yogyakarta, Indonesia, 2) the development of a quantitative an understanding of the relationships or linkages between weather anomalies associated with El Niño/Southern Oscillation (ENSO) in Indonesia and variability in dengue transmission, and 3) the development of a dengue control strategy based on targeted source reduction and a dengue early warning system (EWS) that is will be evaluated in Indonesia in 2004 with private Indonesian funding.

Background

Text of original grant proposal to NOAA-OGP

The original proposal without budget is included below as background information.

Title

Dengue and El Niño Southern Oscillation Events in Yogyakarta, Indonesia: Historical Correlations, Mechanisms, and Recommendations for Control using Source Reduction.

Goal

The overriding objective is to better understand the linkages between various weather parameter anomalies associated (ENSO) events and the dynamics of epidemic transmission of dengue. Specifically, this proposed research will attempt to 1) establish temporal correlations between reported dengue cases and seroconversion rates in Yogyakarta, Indonesia and weather anomalies associated with ENSO events, 2) provide a detailed elucidation of the biologic mechanisms responsible for such linkages, and 3) provide recommendations for a community-based breeding source reduction program that would utilize NOAA's ENSO forecasts.

Background

Dengue viruses are transmitted between humans in the urban environment almost exclusively by the mosquito, *Aedes aegypti* (L.). This mosquito breeds in artificial containers such as discarded tires, water storage drums and cisterns, and other miscellaneous containers. Temperature, saturation deficit, and rainfall influence, by various known mechanisms, the dynamics and characteristics of the vector population; temperature strongly influences the rate of viral dissemination within the vector. These mechanisms are key determinants producing the observed seasonality and geographic distribution of transmission in tropical and neo-tropical dengue-endemic locations.

Briefly, the mechanisms linking transmission and weather are as follows:

Abundance and hydrology of breeding containers. Breeding containers are either filled by rain or maintained by the homeowner. In the case of rain-filled containers, precipitation influences their abundance in locations such as Indonesia where there are many discarded containers in the domestic environment. Temperature and humidity are key factors influencing the rate of water loss. Combined, rainfall and saturation deficit interact with the abundance of receptacles to determine breeding container abundance and water fluctuations within the containers, a factor that influences the timing and success of egg hatch.

Developmental rates and characteristics of vector life stages. Temperature is a key determinate in the rate of development of embryos within the egg, larvae, and pupae. The length of the gonotrophic cycle, the process of taking a blood meal, its digestion, the formation and deposition of eggs is also influenced by temperature. This influences the dynamics of the vector population and the rate of blood feeding, a factor related to transmission potential. Temperature also influences the size of the adult female with higher temperatures being associated with smaller females that have a higher probability of having a requirement of double feeding within the gonotrophic cycle, a factor also related to transmission potential.

The extrinsic incubation period (EIP). The EIP is the time required for virus, acquired when taking a blood meal, to disseminate throughout the body of the mosquito; a disseminated infection results in the presence of virus within the salivary glands where it is available for transmission. EIP is strongly and non-linearly related to temperature.

Vector survivals. Daily survival rates of adults and eggs are adversely affected by high temperatures and saturation deficits; temperature extremes can also reduce larval and pupal survival. This influences vector dynamics, but more importantly, influences transmission potential of the female as transmission potential is a function of the proportion of females surviving long enough to complete the extrinsic incubation period (EIP).

The dengue transmission models. The Container Inhabiting Mosquito Simulation Model (CIMSiM) and Dengue Simulation Model (DENSiM) are validated, mechanistic computer simulation models that account for the factors listed above. They employ country- or location-specific information on daily weather, the types and abundances of breeding containers, human birth and death rates, and a host of other factors that enable simulating human and vector population dynamics, age- and serotype-specific profiles of dengue antibody, and transmission through time. They have been used for epidemic and climate change evaluations, vaccine-site characterization, control operations, and basic and applied research on various facets of transmission. Articles dealing with these models and their use include the following:

1. Focks DA, Haile DG, Daniels E, Mount GA, 1993. Dynamic life table model for *Aedes aegypti* (L.) (Diptera: Culicidae). Analysis of the literature and model development. *J Med Entomol 30:* 1003-1017.

2. Focks DA, Haile DG, Daniels E, Mount GA, 1993. Dynamic life table model for *Aedes aegypti* (L.) (Diptera: Culicidae). Simulation results and validation. *J Med Entomol 30:* 1018-1028.

3. Focks DA, Daniels E, Haile DG, Keesling JE, 1995. A simulation model of the epidemiology of urban dengue fever: Literature analysis, model development, preliminary validation, and samples of simulation results. *Am J Trop Med Hyg 53:* 489-506.

4. Focks DA, Chadee DD. 1997. Pupal survey: An epidemiologically significant surveillance method for *Aedes aegypti*: An example using data from Trinidad. *Am J Trop Med Hyg 56:* 159-167.

5. Jetten TH, Focks DA. 1997. Changes in the distribution of dengue transmission under climate warming scenarios. *Am J Trop Med Hyg 57:* 285-297.

6. Martens WJM, Jetten TH, Focks DA. 1997. Sensitivity of malaria, schistosomiasis and dengue to global warming. *Climate Change 35:* 145-156.
7. Patz JA, Martens WJM, Focks DA, Jetten TH. 1998. Dengue fever epidemic potential as projected by general circulation models of global climate change. *Environ Hlth Perspectives 106:* 147-152.
8. Focks DA, Brenner RJ, Chadee DD, Trosper J. 1998. The use of spatial analysis in the control and risk assessment of vector-borne diseases. *Am Entomologist 45:* 173-183.
9. Focks DA, Brenner RA, Daniels E, Hayes J. 2000. Transmission thresholds for dengue in terms of *Aedes aegypti* pupae per person with discussion of their utility in source reduction efforts. *Am J Trop Med Hyg. 62:* 11-18.

Methods to establish linkages between ENSO events and transmission.

Datasets: There are 3 datasets pertaining to transmission in Yogyakarta, Indonesia.

1. The first dataset includes an initial age- and serotype-specific baseline serosurvey of 1,837 school children aged 4-9 years conducted by the US Navy in 1995. In subsequent years, seroconversions were monitored annually in this same cohort until 1998. This dataset provides extremely accurate estimates of annual rates of transmission in Yogyakarta by serotype. This series is arguably the best dataset of its type currently extant for dengue in Southeast Asia.
2. The second dataset is a time series of the number of patients reporting to Yogyakarta medical clinics with diagnoses consistent with severe primary or secondary dengue infections. This dataset provides an indication of dengue transmission on a monthly basis back to 1985; it is based on a review of clinical records.
3. The third dataset consists of the results of 4 entomologic/demographic surveys of >300 houses in Yogyakarta conducted in 1996 and 1999 by the US Navy and Indonesian cooperators. Each year, a pair of surveys were conducted, corresponding to the wet and dry seasons; the same houses were visited in each of the 4 surveys. Data collected include the number of people per household, the number and type of *Ae. aegypti*-breeding containers present and the number and identification of pupae in each. Combined with the serosurvey information, theses data allow for the parameterization of both CIMSiM and DENSiM.

Analysis methods

Anecdotal accounts indicate for Indonesia, and perhaps Vietnam and Cambodia, that a relationship exists between ENSO-associated weather anomalies and dengue transmission. To attempt to establish temporal correlations between transmission in Yogyakarta and weather anomalies associated with ENSO events, two techniques will be used. If successful, these relationships would be extremely useful in developing an early warning system for dengue.

1. Standard time series analysis will be used to develop statistical relationships between weather (and its lags) and monthly cases for the years when case data are available in Yogyakarta, Indonesia. The product here will be statistical equations of the form *Incidence of Cases at time t as a function of various lags of Temperature, Rainfall, and Saturation Deficit* on a monthly basis.
2. Model vector and transmission dynamics using CIMSiM and DENSiM. These models will be parameterized for Yogyakarta, Indonesia using the detailed container/demographic survey

data. The product here will be an estimated incidence of infection (a surrogate of serious, reported dengue illness, i.e., cases) over time in response to weather. The models permit examining the relative impact of weather on transmission.

Expected Results

1. *Identification of linkage mechanisms and their relative significance.* CIMSiM and DENSiM will be used to provide an identification and quantification of the various biologic mechanisms responsible for weather/transmission linkages. We can address the following issues:
   a. How does rainfall, temperature and atmospheric moisture influence the abundance of breeding containers? Can ENSO-related weather anomalies be associated with observable changes in breeding container or *Ae. aegypti* abundance?
   b. What is the relative significance of variations in EIP, adult size, gonotrophic development rate, and survival, as influenced by seasonal and interannual temperature variation, on transmission?
   c. Can ENSO- and non-ENSO-related weather anomalies be associated with rates of transmission?
2. *Provide information necessary for epidemic control.* Insecticide-based control strategies have been shown to be ineffective yet continue to be used, perhaps promoted more by inducements by suppliers of insecticides than effectiveness. What is needed are site- and weather-specific recommendations on the levels of targeted source reduction required to prevent epidemic transmission. Transmission thresholds for dengue in terms of the number of *Ae. aegypti* pupae per person as a function of temperature and seroprevalence of dengue antibody have recently been developed (see references above). This analysis will provide information that will permit a community-based and targeted source reduction control strategy with known end points. The following items will be supplied:
   a. The relative contributions to the vector population of the various types of containers.
   b. The degree of source reduction by container type necessary to preclude epidemics. It may be possible to make these estimates for ENSO and non-ENSO years.
3. *Investigate the possibility of predicting epidemic years on the basis of ENSO forecasts.* Using the results of the weather-based time series and CIMSiM/DENSiM analyses, an evaluation of the possibility of developing an early warning tool for dengue epidemics based on ENSO forecasts will be made.

Data requirements

1. *Weather data:* Daily weather will be required for Yogyakarta that includes the following parameters: maximum and minimum surface air temperatures, rainfall, and relative humidity (or saturation deficit). Currently, we have complete daily data for Yogyakarta for the years 1995-1997. Required would be for years 1985-1995 and 1998. These periods reflect times when case or seroprevalence data exist. We will assume these data will be provided by NOAA.
2. *Case data:* Currently available are annual rates of seroconversions in children aged 5-9 yrs in Yogyakarta from 1995 through 1998; we currently have the 1995 baseline survey results and the seroconversions for 1996. Hospital records of cases exist from about 1985 and may

also be available through Dr. Ross Graham, U.S. Navy. we will be responsible for obtaining the case and seroconversion information.

3. *Container and demographic information.* Four comprehensive surveys of >300 houses were conducted in Yogyakarta in 1996 and 1999 providing information sufficient for this project on the types of containers present and their associated standing crops of pupae; demographic surveys were completed at the same time. We currently have these data.

[End of original proposal.]

Results

Results from Prior Research

Transmission models

Recently, there has been a movement in the epidemiological community to recognize the pervasive influence of the environment and climate on various vector-borne diseases. The efforts of Martens *et al.* [1] and Patz *et al.* [2], for example, have documented substantial ties of disease activity to environmental features and climate trends for dengue, schistosomiasis, and malaria; the work of Bouma *et al.* [3] establishing statistical relationships between weather anomalies associated with El Niño and malaria in Colombia is especially encouraging in the context of developing early warning/mitigation systems for weather-driven infectious diseases.

Recognizing these ties, mathematical epidemiologists and public health specialists are beginning to construct disease models incorporating environment and climate parameters. A number of researchers have recently been involved in these types of studies on the dengue system and have developed simulation models and estimates of transmission thresholds. [4, 5, 6, 7, 8] These results have had a degree of successful and are increasingly being accepted by the public health community. The algorithms of the dengue models [4, 6] take into account key factors known to influence dengue epidemiology; the result is a software tool orientated toward site-specific simulation and designed to be used by researchers and public health practitioners alike. The algorithms have been validated at multiple sites in Asia and the Americas.[6] The transmission thresholds were derived from the models and are currently being evaluated in Viet Nam and Peru with funding from WHO and the US National Institutes of Health (NIH), respectively.[8] The published thresholds can be used in tropical locations to predict disease vulnerability, assess control measures, and provide guidance in targeting the especially important classes of breeding containers. The recent development of the pupal/demographic survey coupled with estimates of transmission thresholds, make the results of simulation studies with the dengue models available to operational control programs in the developing world.[7, 8]

Transmission thresholds and the pupal / demographic survey

For dengue, the expense and ineffectiveness of drift-based insecticide aerosols to control dengue epidemics has led to suppression strategies based on eliminating larval breeding sites.[7] With the notable but short-lived exceptions of Cuba and Singapore, these source reduction efforts have met with little documented success. Failure has chiefly been attributed to two factors: inadequate participation of the communities involved, and a strategy that entailed destruction or treatment of virtually every breeding container in the environment. The recently-developed transmission thresholds for dengue based on the standing crop of *Ae. aegypti* pupae per person[8] were developed for use in the assessment of risk of transmission and to provide targets for the actual degree of suppression by type of breeding container required to prevent or eliminate transmission in source reduction programs. When coupled with field observations from pupal/demographic surveys (as reported herein for Yogyakarta, Indonesia), it is possible for the first time for control specialists to know how important the various types of containers in the environment are in terms of contributing to the transmission threshold. This strategy of going after the types of containers most responsible for the majority of adult vector production and hence transmission, e.g., outdoor drums and tires vs. typically low producing indoor vases and domestic containers, is currently being evaluated with WHO funding in Viet Nam. More recently and as a further indication of interest by WHO/UNDP/World Bank Special Programme for Research and Training in Tropical Diseases (TDR) has commissioned a review article on the current state of the science for entomological surveying for dengue risk assessment and control.[9] Central in this document are the concepts of the pupal/demographic survey, transmission thresholds, and targeted source reduction and control of especially productive containers. There is a growing recognition that adherence to the current strategy of attempting to eliminate all containers, irrespective of productivity is doomed to continued failure.

Recent efforts to evaluate the utility of the pupal/demographic survey for control

In addition to the WHO-funded evaluation in Viet Nam, the TDR has become involved in examining the usefulness of the pupal/demographic survey used in conjunctions with transmission thresholds. TDR/WHO commissioned a TDR document describing this method.[10] In the summer of 2003, Dr. Mike Nathan of WHO/Geneva and myself developed a request for proposals (RFP) to evaluate the utility of the pupal/demographic survey to develop targeted source reduction/control programs. Thirty-one proposals were submitted and in October of 2003, 9 proposals were funded by TDR for starts in 2004. Evaluation projects will be conducted in Cuba, Peru, Venezuela, Mexico, Colombia, Viet Nam, Thailand, India, and Kenya.

1. Identification of linkage mechanisms and their relative significance

1. a. First question: How does rainfall, temperature and atmospheric moisture influence the abundance of breeding containers?

The purpose of this section (1. *a*.) is to provide an analysis of four annual pupal/demographic surveys conducted in Yogyakarta during 1996-1999 highlighting the epidemiological significance of the twenty-some types of *Ae. aegypti*-breeding containers in the environment. This is one of the existing but datasets described in the original proposal and highlighted for analysis. From this analysis summarized below and using the estimates of transmission thresholds for dengue, we propose to develop a targeted source reduction/control strategy for Yogyakarta that will require substantially less effort than the traditional community-based efforts without targeting where the goal is to control or eliminate all containers irrespective of their contribution to the adult population of *Ae. aegypti* (the subject of section 2 below). This analysis also provides insight into the influence of rainfall on productivity of *Ae. aegypti.* It also identifies the most epidemiologically important container types. The follow sections describe the study site, the survey methods, and the results of the analysis.

Study site

Yogyakarta, a city of over 500,000 people, is the provincial capital of Yogyakarta located in central Java. The Province is divided into administrative districts called *kabupatans*. Each district is divided into progressively smaller units beginning with sub-districts called *kecamatans*, and these, in turn, divided into *kelurahans*, and further still, into *ruken warga* (RW), and finally into *ruken tetanngga* (RT), the smallest administrative unit composed of approximately 50 families each. The study site was located in the Kecamatan Gondokusuman, within Yogyakarta city itself. The actual study coverage area covered approximately 6.34 ha, from which 323 houses were selected and subsequently sampled over 4 time periods. Houses were selected using a computerized multistage random sampling technique based on number and distribution of previous dengue cases that occurred in the same area. Data was derived from a recent study conducted in the same area [11]. An average of 5 houses were chosen from each RW where a dengue case occurred and included 64 RW's distributed among 5 kelurahans (Kota Baru = 4 RWs; Terban = 11 RWs; Baciro = 21 RWs; Klitren = 16 RWs, and Demangan = 12 RWs). The location of each sampled house was provided coordinates in 1999 using a handheld geographical positioning (GPS) device. Demography data were taken from each house, including number of permanent residents, house size and land area. Climatologic data (daily rainfall and maximum/minimum ambient temperatures) were obtained from the local Meteorology and Geophysics Agency (Station Bulaksumar, University of Gadjah Mada).

The pupal / demographic survey

Each premise was sampled consecutively for immature stages of container-breeding mosquitoes during 4 different time periods between 1996 and 1999, with 2 sample surveys during wet seasons and 2 during the dry periods of the year.[a] A team of three to four people would visit each house and carefully inspect inside and around the outside perimeter all natural and artificial containers for preimaginal stages of mosquitoes. The number and type of containers present at each house were recorded as well the number of residents. The presence or absence of mosquito larvae in each container was recorded without regard to number present. Collections concentrated on quantifying pupal abundance by type of container. With the aid of a flashlight, handheld finemeshed netting devices and pipettes were used to remove all pupae from the container with captured specimens placed in white trays for easy observation. While in the field, all pupae would be first immobilized using hot water supplied from a thermos and immediately placed in labeled plastic bags containing 70% ethyl alcohol and sealed. Bag labels included house number, container type, location (indoor or outdoor) and number of pupae collected. Additionally, all information, including lot and house size was hand recorded in a field logbook and later transcribed into a computerized database. The only water-holding containers not surveyed in this study were residential wells which are known to harbor *Ae. aegypti* and *Culex quinquefasciatus* Say larvae.[12]

Specimen identification

Preserved pupae were returned to the laboratory for identification. Using an illustrated key developed for this purpose,[13] pupae were examined using a stereomicroscope and easily identified to species and sex. For the purposes of this study, pupae were identified as either *Ae. aegypti*, *Aedes albopictus* Skuse, or *Cx. quinquefasciatus* with all other pupae identified only to genus.

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[a] Collection Dates: Dry season: 8-22 May 1996, Wet: 23 January-7 February 1997, Dry: 15-30 September 1998, and Wet: 30 March-19 April 1999.

Results of Yogyakarta analysis

With only a few exceptions, the 4 pupal/demographic surveys conducted in the Kecamatan Gondokusuman censused the same houses ca. 316 houses each year. Residents associated with these houses numbered approximately 2,800 (see Table 1 for summary data). Each exhaustive survey collected pupae from the ca. 3,000 water-filled containers associated with the study houses. Approximately 5.5% of the containers were positive for one or more pupae of *Ae. aegypti*, *Ae. albopictus*, or *Cx. quinquefasciatus*. Approximately ten times more *Ae. aegypti* pupae were recovered than *Ae. albopictus* (ca. 1,600 vs. 160); *Cx. quinquefasciatus* was rarely found in the sites being examined. Average temperatures during the dry and wet season surveys were not substantially different, averaging 28.0 and 27.2°C, respectively (Figure 1). However, accumulated rainfall for the 60 days prior to each dry season survey were about 10% of wet season accumulations (ca. 84 vs. 794 mm).

Types and numbers of water-filled containers as a function of season

A total of 71 different types of water-filled containers were observed during the 4 surveys; many of these types, however, were only seen once or at most only a few times during the surveys. The 3, 5 and 11 most common types of containers accounted for >60, >75, and 90% of all water-filled containers, respectively (Table 2). Some types were exclusively found either indoors or outdoors and others could be seen in both locations. By location, 34 types were observed indoors and 66 types outdoors. Rainfall accumulations preceding the surveys influenced the number of types of containers in the environment (Table 2). During the 2 dry season surveys, a total of 26 and 40 different types were observed indoors and outdoors, respectively; the corresponding numbers for the 2 wet season surveys were 29 and 60 different types, respectively. However, somewhat surprisingly, the average number of water-filled containers was largely independent of the season of the surveys (Table 1); the average number of water-filled containers in the environment was 2,732 and 2,770 for the dry and wet season surveys respectively.

Numerically, the most common types of containers observed were (in descending frequency) bird watering dishes, buckets (*ember*), water storage container in water closet (*bak mandi*), large water tanks (*bak air*), plastic water containers (*tempayan*), and large water storage containers. These particular containers accounted for ca. 80% of all water filled containers. Thirty-five of the 71 types observed were never found positive for the pupae of any species in any of the surveys. Table 2 provides a list of the 24 most common container types in descending order of abundance. Of the 9 most common types, accounting for 87% of all containers, there were no significant changes in abundance as a function of season suggesting that the most common types of containers are not rain-filled but filled manually. Those container types listed in Table 2 that are more commonly found in the wet season are also those that are located primarily outside of the residence, e.g., flower pots, plant axils, tin cans, and tires.

Standing crop of pupae as a function of season and type of container

The average proportion of containers with larvae and pupae in the dry season was 0.128 and 0.047, respectively; the corresponding proportions for the wet season were 0.173 and 0.061. Of the pupae collected in all surveys, independent of season, *Ae. aegypti* accounted for 89.8%, *Ae. albopictus* 9.0%, and *Cx. quinquefasciatus* 1.2% of the total (Table 1). A summary of pupal collection as a function of survey, container location, species of mosquito, and season (Table 3) indicates that *Ae. aegypti* can be found in indoor and outdoor containers and that the number of pupae coming from outdoor containers increases during the rainy season; the standing crop of

Ae. aegypti indoors is remarkably constant and independent of season. Outdoor breeding accounts for virtually all additional production during the rainy season. In contrast, *Ae. albopictus* pupae are essentially found only outdoors and in rain-filled containers. It is therefore not surprising that the average standing crop of *Ae. aegypti* is somewhat less a function of rainfall (dry season average—1,312 vs. wet season—1,862 (an increase of ca. 42%) than *Ae. albopictus* where the dry season average—38 rose to 281, an increase of 640%. Table 4 provides an average of total pupal collections for the two seasons by mosquito and location. While the numbers collected are low and preclude confident statements, *Cx. quinquefasciatus* in these surveys is only found outdoors and its abundance seems independent of rainfall. *Aedes albopictus* abundance is a strong function of rainfall and is only found outdoors.

The total number of *Ae. aegypti* pupae recovered in the 4 surveys were combined to provide the best estimate of production by class (Figure 2). The total number of *Ae. aegypti* pupae in each of the types of containers highlights an important point: The epidemiologic importance of a class of container is not simply a function of the abundance of the container, but rather the product of the container's abundance and productivity (Table 5). The water storage containers located in water closets (*bak mandi*) account for 22% of all containers but 50% of all *Ae. aegypti* pupae. The classes "*large water container*" (*bak air*) and *tire* account for 6 and 1% of all containers, yet the are responsible for 13 and 6% of all pupae, respectively. The large water tank (12% of all containers) contributes essentially nothing to *Ae. aegypti* production.

Simulation studies on the influence of temperature on container productivity

In temperate locations, *Ae. aegypti* overwinters in the immature stages and seasonal variation in adult abundance clearly reflects the key role of temperature on immature development. However, under tropical conditions, adult abundance varies not with temperature but with variation in the abundance and productivity of water-holding containers; container productivity is limited, not by temperature or oviposition, but by density-dependent larval survival which is ultimately driven by the amount of food falling into or formed photosynthetically within the container. This is consistent with both CIMSiM's rather constant estimates of adult abundance from manually-filled containers under conditions of constant temperatures of 22 to 32°C (not shown). In light of this, going back to the Bangkok story of the investigation into the cause(s) of seasonal variation in incidence of dengue, we should not be surprised to read that the field work of Sheppard *et al.* indicated no seasonal trends in adult survival.[14]

Summary regarding the role of rainfall, temperature and atmospheric moisture on the production of vectors

These field and simulation studies provide empirical answers to the influence of rainfall on adult production and its distribution among the various types of containers, and this is sufficient to develop a targeted control strategy that will reduce the system below transmission threshold. This will be presented in section 2 below entitled "Provide information necessary for epidemic control."

1. a. Second question: Can ENSO-related weather anomalies be associated with observable changes in breeding container or Ae. aegypti abundance?

With the current data sets, we cannot answer this question with regard to changes in breeding containers or *Ae. aegypti* abundance. The period of 1997-98 saw the development of the largest or most intense ENSO event in observed history. We note in section 1. *a*. that both of these variables are influenced by seasonal rainfall amounts. However, the 30- or 60-day rainfall accumulations (Figure 1) preceding each dry season survey are roughly the same, as are the accumulation during the 2 wet season surveys. However, anomalously high temperatures during the winter of 1997-98 associated with the ENSO event will be related to transmission in the next section (1. *c.*).

1. b. What is the relative significance of variations in EIP, adult size, gonotrophic development rate, and survival, as influenced by seasonal and interannual temperature variation, on transmission?

These are questions that were addressed with simulation studies conducted with funding from this grant. We begin with a variable not in the list above, saturation deficit, and include it because it was an inadvertent omission in the grant proposal.

Atmospheric moisture's influence on survivals

The drying power of the atmosphere, as measured in saturation deficit (mBars pressure), reflects the combined influence of temperature and relative humidity. The dengue system (and models) are influenced by saturation deficit in several ways. In CIMSiM, atmospheric moisture influences evaporation rates from containers along with certain characteristics of the container—their size, shape, and exposure to direct sunlight. Also, deficits greater than ca. 10 mBars progressively reduce survival of newly-laid eggs and adults. The impact on egg survival under very dry conditions is minimal and, with the possible rare exception of breeding in exposed lime rock solution holes adjacent to beaches, is easily compensated by subsequent density-dependent larval survival. Based on CIMSiM, only at particularly hot and dry continental locations such as Ouahigouya, Burkina Faso are conditions such that adult survival is reduced by excessive temperatures and high saturation deficits. Here, the dynamics and abundance of adults and immatures would not be materially different under milder conditions, again, primarily from the resilience in the entomological system from density-dependent larval survival. However, the shortened adult lifespan significantly reduces transmission in simulation studies (not shown).

For Yogyakarta, average monthly saturation deficits are less than 10 mBars and the models indicate that atmospheric moisture does not limit any portion of the dengue transmission system. This is consistent with the conviction that atmospheric moisture is not a key variable influencing dengue dynamics in Southeast Asia.[6]

Productivity of containers as a function of temperature

In temperate locations, *Ae. aegypti* overwinters in the immature stages and seasonal variation in adult abundance clearly reflects the key role of temperature on immature development. However, under tropical conditions, adult abundance varies not with temperature but with variation in the abundance and productivity of water-holding containers; container productivity is limited, not by temperature or oviposition, but by density-dependent larval survival which is ultimately driven by the amount of food falling into or formed photosynthetically within the container. This is consistent with both CIMSiM's rather constant estimates of adult abundance from manually-filled containers under conditions of constant temperatures of 22 to 32°C (not shown). The insight of the models is consistent with the field work in Bangkok indicating that there were no seasonal trends in adult densities.[14]

The influence of temperature-driven variation in the extrinsic incubation period (EIP) and gonotrophic cycle length

While temperature may not influence container productivity in the tropics (preceding question), could it influence adult survival, an important determinant in transmission intensity? (This is another question inadvertently omitted in the grant proposal.) The answer is no, survival is not a function of temperature in tropical locations.[6, 14] However, temperature does play a key role in dengue dynamics through its role influence of two other variables of the dengue system, EIP and gonotrophic cycle length discussed below.

Under moist, tropical field conditions such as Yogyakarta, where the major mortality sources are accidents such as encountering a spider's web, the probability of surviving a single day (Sa) is constant and independent of temperature. Experiments to measure this parameter in the field are notoriously noisy but a consensus value is somewhere between 0.87 and 0.91 per day under conditions without temperature or moisture deficit extremes such as for most locations in dengue-endemic regions, e.g., Southeast Asia.[14] The integral of Sa^t provides the average lifespan of the female, for Sa = 0.89, the average lifespan is ca. 8.6 days.[b] Keeping in mind that the resulting age distribution is declining exponentially with age, it is easy to see that numerically, while most emerging females die at an early age, the tail of this age distribution contains the rather rare but older individuals which have the potential to transmit. The length of time required for newly infected female to become infectious, the extrinsic incubation period (EIP), is a non-linear function of temperature; the same can be said regarding the length of the gonotrophic cycle. Both of these relationships are presented in Table 6.

Notice that if a female takes an infectious bite on her first day of life, the length of time required for her to have a disseminated infection is EIP plus one day—a substantial portion of the average lifespan; most will not pass on virus before death. Moreover, once disseminated, the probability of transmitting virus will vary with how often they bite which is related to the length of gonotrophic development period. Figure 2 presents an estimate of the average number of potentially infectious replete feeds per newly-emerged female as a function of temperature and daily survival probability. This figure makes, for the purpose of comparisons, the unrealistic assumption that all mosquitoes take an infectious blood at one day of age. The actual number of potentially infectious bites per replete feed is unknown and may be as high 2 or 3 or more interrupted feeding attempts with resumption on the same or different host.[6] From an epidemiological perspective, it is important to realize that a temperature-related doubling of the expected number of potentially-replete feeds, the consequences of 2 or 3 degrees warmer temperatures is equivalent to a doubling of the density of *Ae. aegypti*. While temperature plays a role in most facets of transmission dynamics, its influence on the speed on viral dissemination and frequency of biting is a key regulating force entraining seasonal variability. And indeed, the field work of Pant *et al.* allowed them to hypothesize that the source of the seasonality seen in dengue in Bangkok was due, not to rainfall variability leading to adult abundance seasonality, nor to excessively high temperatures and/or dryness leading to a reduced adult survival, but to temperature-related variability in the infectiousness of *Ae. aegypti* females through the agency of EIP and gonotrophic development rates.[15] This is the same conclusion reached through an analysis with CIMSiM/DENSiM of the

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[b] $\int_{t=1}^{t=\infty} Sa^t \, dt$

Bangkok situation.[6] Simulation analysis conduced for this grant indicates that these two temperature-driven variables are major forcing functions in the dynamics of dengue in Yogyakarta. This will have practical implications for the development of practical early warning systems useful for control operations (subject of next section).

1. c. Can ENSO- and non-ENSO-related weather anomalies be associated with rates of transmission?

History of dengue in Indonesia

Dengue and dengue haemorrhagic fever (DF/DHF) was first observed in Indonesia in 1968 in Surabaya and Jakarta. While this initial epidemic involved less than 60 cases, the case fatality rate exceeded 40%. Since then the incidence of DF/DHF has increased dramatically in Indonesia and has spread geographically to all regions of the country. The DHF incidence fluctuates monthly and reaches its peak in December and January every year except in big cities such as Jakarta, Bandung and Surabaya, where the highest incidence occurs in April and May.[16] Today, dengue is the eighth leading cause of hospitalization among Indonesian children.[17] Similar trends of progressively larger epidemics interspersed with quieter years in the neighboring countries of Cambodia, Myanmar, Laos, Thailand, and Vietnam reflect waxing and waning human population "herd" immunity, urbanization, the extensive movement of people, and the influence of weather anomalies associated with El Niño/Southern Oscillation (ENSO) events. Early in the year 1998 witnessed the largest epidemic on record in Indonesia with 72,133 reported cases, 1,414 deaths; the case fatality rate (CFR) in this epidemic was relatively low, 2.0%, reflecting several decades of improved clinical management.[17] In 2001, total cases (DF and DHF) and deaths reported were almost 20,000 and 180, respectively.[18]

ENSO-related temperature anomalies associated with dengue epidemics

Sufficiently high ratios of adult *Ae. aegypti* to humans, low herd immunity levels, and adequate temperatures are necessary but not sufficient to produce an epidemic. There is interannual variability in the types of dengue viruses circulating in a region (Figures 3 and 4).[19] We will see below that predicting dengue epidemics (section 3) uses two predictive variables, temperature (for the reasons cited above) and lagged cases—a proxy for the current types of virus circulating and the nature of herd immunity interacting to lead to an increase in sequential infections associated with DHF and dengue sever shock (DSS) pathology, viz., cases counted by the health system. But before we describe the relationship with ENSO-related temperature anomalies and transmission, we must first describe a little appreciated phenomenon, the temporal lag between high temperatures and epidemic transmission.

Lags between factors favoring transmission and cases

Dengue epidemics obviously involve one person's infection leading to another's; the number of infections resulting in the next cycle from a single individual is commonly referred to as R_0. As long as R_0 is greater than one, the epidemic grows exponentially at a rate proportional to this ratio. The magnitude of R_0 is dynamic, reflecting the integration of the host of factors influencing dengue dynamics. Higher temperatures shorten EIP and the gonotrophic cycle and are thus a factor tending to increase R_0 as would rainfall leading to more *Ae. aegypti* in the case of Yogyakarta (Tables 1 and 3). High levels of herd immunity, effective spraying that shortens adult survival, or window screens limiting host access would favor reductions in R_0. Dynamically accounting for the influences of the various factors through time is a chief activity of accounting software such as CIMSiM/DENSiM. Table 7 and Figure 5 present three examples of how increasingly high initial values of R_0 in the months preceding an epidemic can result in substantially more infections in the subsequent epidemic phase when conditions may have actually moderated and R_0 values are lower. This produces a *lag* between conditions promoting transmission and the subsequent realization in the epidemic when the number of infections is high.

Table 8 provides correlation coefficients between monthly cases and lagged monthly cases, average temperature, rainfall, length of the gonotrophic cycle and the extrinsic incubation period (EIP) for dengue in Bangkok, Thailand from 1966-1994; we use this data set instead of Yogyakarta because of its unique length permits such analysis. It is not surprising that cases are highly autocorrelated going back for at least four months; anomalously high (or low) prevalence this month reflects unusually large (or small) prevalence last month, for cases, through the agency of *Ae. aegypti*, give rise to subsequent cases. The lack of substantive correlation between current cases and current weather, temperature and rainfall and their lags going back one, two or three months may come as a bit of a surprise to people who are not acquainted with dengue data—this phenomenon reflects the fact that epidemics take several months to develop to a level where they are recognized as a result of antecedent conditions as described above.[20] To be truthful, there are some non-trivial correlations between cases and the preceding two months' rainfall suggesting that, as in Yogyakarta, in the Bangkok metropolitan area, not all containers are manually-filled. With regard to collaborating the story of antecedent conditions being key determinants of epidemics, the peaks in correlations between cases and temperature, gonotrophic cycle length, and EIP (as estimated with CIMSiM and DENSiM using historical weather data) three and four months earlier are important. Epidemics, under these conditions of constantly endemic virus, are entrained by environmental determinants at play months before the health community is aware that a nascent epidemic is building. And, epidemics can and do occur under weather conditions less than optimal for intense transmission.

Summary regarding ENSO-related weather anomalies and transmission

If the foregoing analysis is substantively correct, we can conclude in the affirmative that ENSO-related weather anomalies can indeed, *in regions where regular, substantial anomalies are associated with ENSO state*, be associated with transmission dynamics—always keeping in mind the necessary but not sufficient caveat above. Early warning systems, as we will see below, will necessarily involve information on past cases as well as some proxy for temperature, be it sea surface temperature anomalies or ENSO forecasts. I am currently working with Dr. Lisa Goddard at the IRI Climate Prediction Center in an attempt to use NOAA's ENSO forecasts in lieu of the SST anomalies in the EWS for Indonesia.

2. Provide information necessary for epidemic control

Background on dengue control efforts in Indonesia

The World Health Organization's Regional Office for South-East Asia conducted an external review of the dengue/dengue haemorrhagic fever prevention and control program of Indonesia in June of 2000.[17] The following thumbnail history of the Indonesian dengue prevention and control program reflects their report.

The strategies to control dengue in Indonesia have been modified considerably over the past three decades. Initially, adult control using perifocal space spraying of insecticides with portable and vehicle-mounted thermal fogging and ultra low volume (ULV) machines was the government's recommended method for most areas. The protocol specified treatment within a 100-meter radius of reported DHF cases. In the decade of the 1980s, the strategy changed to include the addition of extensive larviciding using temephos on sand granules. Here, the protocol was to treat all breeding sites in dengue-endemic urban areas a single time each year, timed to proceed the onset of the transmission season. This protocol was subsequently modified to target only those urban areas reporting DHF for three consecutive years; in these locations, re-treatments were scheduled with a frequency of three months. This selective program was in place between 1986 and 1991. Beginning in 1992 and continuing until the present, the national strategic emphasis has been larval control involving community efforts, health education, and intersectoral coordination. Currently, national efforts have focused on organizing working groups at the village level under the general guidance of the local health center personnel. This programme, called Bulan Gerakan (or 3M), emphasizes intensive health education using mass media, women's groups and school children, community-based breeding source reduction, and door-to-door house inspections to monitor for larvae, and to clean containers and apply temephos as necessary. An important member of the *3M* programme is the Family Welfare Education Women's Movement (Pendidikan Kesejahteraan Keluarga or PKK). The role of the *PKK* workers is education of the house-owner about larval inspections, methods to safely store water, and the elimination or cleaning of breeding containers. An additional role of the *PKK* involves community-based group education and monitoring programme results. Finally, health education programmes have been developed for elementary school children and for use with the mass media.

Unfortunately, with only a few notable exceptions, these efforts have not been successful in controlling dengue.[7] However, a pilot project in the City of Purwokerto, aided with modest funding from the Rotary International has shown promise. The approach was organized around a strategy of community partnerships based on *dasa wisma* (ten houses) in several villages in the area. The results were encouraging to the degree that Rotary and others have funded an extension to this effort which will target 11 major urban areas in Indonesia. Patterned after the Purwokerto project, it will include educational programs for the public and medical personnel. The extended project has the endorsement and support of the Indonesian government, the World Health Organization (WHO), and US Public Health Service (CDC).

Our current goal in Indonesia is to build on the effectiveness of the Bulan Gerakan and PKK programs by simply reducing the number of types of breeding containers that must be controlled or eliminated to only a select few that are responsible for most of the adult vector production—targeted source reduction and/or control. Estimating the degree of reduction required and the identification of the particularly important types of container is made possible by some recent developments outlined below. The strategy is based on targeting only the most epidemiological important types of breeding containers. We measure the epidemiologic importance of each type of container in the environment using the statistic, the total standing crop of *Ae. aegypti* pupae per hectare associated with each particular type. We anticipate further reduction in labor by confining control efforts to periods of the year predicted to be epidemic months by a dengue early warning system (EWS) described below in section 3.

2. a. The relative contributions to the vector population of the various types of containers

The first goal in this section was presented in section 1 above in the analysis of the 4 surveys in Yogyakarta—the relative contributions of the various types of containers to the total adult production in the environment. We put it in section 1 because if afforded an answer the question of the role that seasonal variability in rainfall amounts influenced container abundance and productivity. We now proceed to develop a targeted source/control strategy based on transmission thresholds and the absolute contribution to *Ae. aegypti* productivity by container type and ENSO state.

2. b. The degree of source reduction by container type necessary to preclude epidemics

The underlying notion of targeted source reduction is one of selectively attacking the most important types of containers. Field observations cited above suggest the rationale is sound in that containers vary significantly in their production of *Ae. aegypti*. The actual epidemiologic significance of any particular type of container, say discarded tires, is a function of the average standing crop of pupae found in that type and the abundance of that container. Table 9 is an example of how transmission thresholds and the pupal and demographic survey could provide guidance to a targeted source reduction effort. The estimate of the transmission threshold provides an overall target, an upper bound on the number of pupae per person for the environment that insures that viral introductions would result in very little or no transmission. The survey permits estimating the contribution of each type of container and allows, using nothing more than a spreadsheet, conducting what-if analyses of various strategies designed to selective attack different types of containers at various rates of elimination or control based on their epidemiologic importance and how amenable they are to elimination and/or control.

Our example (Table 9) is based on the 4 Yogyakarta surveys described earlier. We develop strategies for temperatures of 29 and 30°C, assuming a seroprevalence rate of 67% from the work of Graham *et al.*,[11] The estimates of the transmission thresholds are 0.38 and 0.26 *Ae. aegypti* pupae per person (taken from Focks *et al.*[8]). At temperatures below 28°C, the combination of existing pupae per person and herd immunity results in the area being below the transmission threshold and epidemic transmission would not expected—this seasonality in threshold as a function of temperature is demonstrated in the seasonality of dengue in Yogyakarta. Dividing the estimate of pupae per person for each type by the two threshold yields estimates of what proportion of the threshold is contributed by each type. In the case of 29°C, for example, the type *Tire* contributes ca. 6% of the threshold whereas the type *Storage WC* accounts for ca. 81% of the threshold. Obviously, if eradication is not in mind, targeting the more important types based on this logic would suggest a focus on the *Storage WC container*. If Table 9 is put into a spreadsheet, evaluating various targeted strategies becomes easy. For the lower temperature, eliminating only the single most productive type, the *Storage WC* would reduce the threshold to below one. For the higher temperature, *Storage WC* and *Water container* (*lg*) would have to be controlled. The other containers could be left alone. Because these are estimates, the operational program we have in mind for Yogyakarta will be more conservative and the top 2 producers, both in the bath/shower room and not used in food preparation, will be targeted in addition to wells using copepods, fish, or abate insecticide. These containers are amenable to these measures by virtue of their size, stability, and use.

3. Investigate the possibility of predicting epidemic years on the basis of ENSO forecasts

At recent (2001 and 2002) World Health Organization dengue workshops in the Southeast Asian region, directors of national anti-dengue programs in Thailand, Vietnam, and Indonesia expressed the operational need for an early warning system (EWS) for that would provide sufficient lead time (1 to 3 months) to permit mobilization of control operations. In response to this need, I developed preliminary EWS's for Yogyakarta on the island of Java in Indonesia and

Bangkok, Thailand; they are based on logistic regression analysis.[21] The predictor variables are sea surface temperature (SST) anomalies over the tropical Pacific and monthly cases of dengue in each city. The predicted variable is the probability of an epidemic year forecast 1 to 3 months before peak transmission season. The Java EWS was sufficiently accurate to be operational. The Yogyakarta EWS gave perfect 1- and 2-month forecasts; the 3-month forecast incorrectly classified one year in the 14-year period of record. This method was inadequate to develop an operational system for Bangkok.

In collaboration with the Department of Statistics, University of Alberta, we have developed a more sophisticated EWS which predicts on a monthly basis, not simply epidemic years, but epidemic months one to five months into the future. This was based on data from 1985—1999 from Yogyakarta.[22] This version has not yet been validated. The plan we are developing for Yogyakarta will focus on the containers mentioned above and control efforts will be confined to those periods of time 2-3 months before a forecast epidemic.

The papers describing the EWS's accompany this document.

Tables

Table 1.

Summary statistics for pupal/demographic surveys conducted in Yogyakarta, Indonesia between 1996 and 1999.

Survey date	Season (Rainfall, avg. temp.) [a]	Number of		Water-filled containers			Total pupae recovered		
		Resi-dences	Inhabi-tants	Total	With pupae	Prop. with pupae	*Ae. aegypti*	*Ae. al-bopictus*	*Cx. quin-quefasciatus*
8-22 May-96	Dry (116, 27.9)	323	2,865	2,345	144	0.061	1,394	43	0
23 Jan-7 Feb-97	Wet (841, 27.0)	319	2,859	3,354	235	0.070	2,136	395	61
15-30 Sep-98	Dry (51, 28.1)	313	2,757	3,118	115	0.037	1,229	33	25
30 Mar-19 Apr-99	Wet (747, 27.3)	310	2,680	3,096	159	0.051	1,588	167	0
Total	—	1,265	11,161	11,913	653	-	6,347	638	86
Average	—	316	2,790	2,978	162	0.055	1,587	160	22

[a] Total precipitation (mm) 2 months prior to survey and average temperature during survey (°C).

Table 2.
The most frequently encountered types of containers during surveys conducted during the dry or wet season in Yogyakarta.

Type	Dry	Wet	Total	Proportion of total	Accumulation
Bird watering dish	670	681	675	0.23	0.23
Bucket	549	619	584	0.20	0.42
Storage in water closet [a]	538	549	543	0.18	0.61
Water tank (large) [b]	251	220	235	0.08	0.68
Plastic water container	196	232	214	0.07	0.76
Water container (large)	112	152	132	0.04	0.80
Clay water container	91	90	91	0.03	0.83
Refrigerator water pan	58	58	58	0.02	0.85
Padasan	41	56	48	0.02	0.87
Flower pot	19	78	48	0.02	0.88
Flower vase	45	41	43	0.01	0.90
Bottle	34	44	39	0.01	0.91
Plant axil	2	77	39	0.01	0.92
Tin can	17	53	35	0.01	0.93
Tire	10	47	28	0.01	0.94
Drinking glass	4	51	27	0.01	0.95
Pool, pond, tank	22	22	22	0.01	0.96
Bowl	3	30	17	0.01	0.97
Drum	11	16	14	0.00	0.97
Fish pond	16	4	10	0.00	0.97
Pan	7	8	8	0.00	0.98
Cover or lid	4	11	7	0.00	0.98
Plate, dish	2	12	7	0.00	0.98
Clay water pot (small)	6	8	7	0.00	0.98

[a] Indonesian: *Bak mandi*

[b] Indonesian: *Bak air*

Table 3.

Summary of the numbers of *Ae. aegypti* and *Ae. albopictus* pupae and containers positive for *Ae. aegypti* and *Ae. albopictus* pupae by location (indoors or outdoors) and survey year and season.

Year	Data	Indoor	Outdoor	Total
1996 (Dry)	*Ae. aegypti* pupae collected	1,006	388	1,394
1997 (Wet)		987	1,149	2,136
1998 (Dry)		858	371	1,229
1999 (Wet)		935	653	1,588
	Averages	947	640	1,587
1996 (Dry)	*Ae. albopictus* pupae collected	0	43	43
1997 (Wet)		39	356	395
1998 (Dry)		0	33	33
1999 (Wet)		2	165	167
	Averages	10	149	160
1996 (Dry)	Containers with *Ae. aegypti* pupae	89	46	135
1997 (Wet)		82	120	202
1998 (Dry)		71	43	114
1999 (Wet)		85	58	143
	Averages	82	67	149
1996 (Dry)	Containers with *Ae. albopictus* pupae	0	12	12
1997 (Wet)		3	61	64
1998 (Dry)		0	4	4
1999 (Wet)		1	27	28
	Averages	1	26	27
1996 (Dry)	Number of wet containers	1,026	1,319	2,345
1997 (Wet)		1,221	2,133	3,354
1998 (Dry)		1,322	1,796	3,118
1999 (Wet)		1,244	1,852	3,096
	Averages	1,203	1,775	2,978

Table 4.
Average numbers of pupae collected as a function of season and location.

Season	Species of mosquito	Inside	Outside	Total
Dry	*Ae. aegypti*	932	380	1,312
	Ae. albopictus	0	38	38
	Cx. quinquefasciatus	0	13	13
Wet	*Ae. aegypti*	961	901	1,862
	Ae. albopictus	20	260	281
	Cx. quinquefasciatus	0	15	15

Table 5.

The frequency of containers by type and the proportion of all *Ae. aegypti* pupae associated with that type. Container types are sorted in descending order of *Ae. aegypti* pupae.

Container type	Proportions of total:	
	Containers	*Ae. aegypti* pupae
Storage in WC	0.217	0.496
Water container (lg)	0.063	0.135
Tire	0.012	0.055
Clay water container	0.041	0.042
Bird water (sm)	0.119	0.041
Bucket	0.150	0.036
Flower pot	0.016	0.036
Trash can	0.000	0.035
Tin can	0.016	0.026
Container	0.081	0.016
Flower vase	0.015	0.014
Fish pond	0.003	0.014
Refrigerator water pan	0.030	0.013
Pool, pond, tank	0.007	0.011
Bowl	0.008	0.005
Drum	0.007	0.005
Water tank (lg)	0.123	0.004

Table 6.

Lengths and daily rates of the extrinsic incubation period of virus within *Ae. aegypti* and the gonotrophic development cycle.[6]

Temperature	EIP		Gonotrophic cycle	
	Rate da^{-1}	Days	Rate da^{-1}	Days
22	0.04	24.0	0.14	7.3
24	0.05	20.0	0.17	6.1
26	0.07	14.0	0.24	4.2
28	0.08	11.8	0.29	3.5
30	0.10	9.9	0.34	2.9
32	0.12	8.4	0.41	2.4

Table 7.

Projected numbers of infections over time as a function of R_o. For illustration, we assume the periods of time between the onset in viremia in the first and subsequent infection cycles are multiples of 17 days. In each example, the epidemic is initiated with a single viremic individual. During the first 4 cycles, the pre-epidemic period (up through day 81), R_o is set to a constant value of 1.5, 2.0, or 2.5 for lines labeled *Cases (1.5, 1.5)*, *Cases (2.0, 1.5)*, and *Cases (2.5, 1.5)*, respectively. The increasing value for R_o could result from slight increases in temperature or greater *Ae. aegypti* abundance, both factors that would increase R_o, for the examples below. For cycles 5 through 10, R_o is set to a constant 1.5 in each case. The purpose of this illustration is to demonstrate that conditions several months before the appearance of large numbers of cases, the epidemic, significantly affect the magnitude of the event. Note in each example that the ratio of new infections in each cycle after day 81 is the same, 1.5, but the *absolute* numbers of infections after additional cycles in the epidemic phase is larger as a function of the number of infected in the pre-epidemic period. This phenomenon is a likely mechanism whereby environmental conditions that promote at the time an increased intensity of transmission but before there are large numbers of infections can become manifest months later as an epidemic under conditions that are less conducive to transmission.

Cycle	*Days*	*Months*	Example 1		Example 2		Example 3	
			Ro	*Infect'ns (1.5, 1.5)*	*Ro*	*Infect'ns (2.0, 1.5)*	*Ro*	*Infect'ns (2.5, 1.5)*
1	1	0.03	1.5	1	2.0	2	2.5	3
2	17	0.56	1.5	2	2.0	4	2.5	8
3	33	1.08	1.5	2	2.0	8	2.5	19
4	49	1.61	1.5	3	2.0	16	2.5	47
5	65	2.14	1.5	5	2.0	32	2.5	117
6	81	2.66	1.5	8	1.5	48	1.5	176
7	97	3.19	1.5	11	1.5	72	1.5	264
8	113	3.72	1.5	17	1.5	108	1.5	396
9	129	4.24	1.5	26	1.5	162	1.5	593
10	145	4.77	1.5	38	1.5	243	1.5	890

Table 8.

Correlations between monthly cases and lagged cases, monthly average temperature (°C), rainfall, length of the gonotrophic cycle (Gono) and the extrinsic incubation period (EIP) for dengue in Bangkok, Thailand from 1966-1994. The length of the gonotrophic cycle and EIP were estimated using CIMSiM and DENSiM using historical weather from metropolitan Bangkok. Correlations greater than ± 0.30 are in italics.

Lag (months)	Correlations between current and past monthly averages				
	Cases	Temp	Rain	Gono	EIP
0	1.00	0.07	0.22	-0.06	-0.09
1	***0.91***	0.18	0.28	-0.16	-0.20
2	***0.74***	0.29	0.24	-0.25	-0.29
3	***0.57***	***0.37***	0.09	***-0.32***	***-0.36***
4	***0.41***	***0.37***	-0.04	***-0.31***	***-0.35***
5	0.27	0.26	-0.14	-0.21	-0.25
6	0.17	0.08	-0.22	-0.05	-0.07

Table 9.

This table lists the most productive types of containers sorted from highest to lowest; only the most productive are listed. *No.* refers to the average number of containers of each type in the survey during the wet season when epidemic dengue transmission is observed. *Prop. of total* refers to the proportion of all *Ae. aegypti* pupae found in each of the types divided by the average total number of pupae observed in the surveys. *Pupae/person* indicates the number of pupae per person associated with that type of container. *Prop. TT* refer to the proportion of the transmission threshold associated with that type. *Sum* refers to refers to the sum of the transmission threshold for that container type and all those below it. For a given temperature, container types are selected for elimination or control from most productive to less productive type until the *Sum* column is < 1.00. At 29°C, only Storage in WC (water closet) needs to be controlled. At 30°C, 2 or 3 types need to be controlled, the *Storage in WC*, *Water container* (*lg*), and perhaps the *Tire* type. See text for further details.

Temp. (°C) and transmission threshold in pupae per person:				29°C—0.38		30°C—0.26	
Type of container	No.	Prop. of total	Pupae/person	Prop. TT	Sum	Prop. TT	Sum
Storage in WC	1,697	0.456	0.31	0.81	1.68	1.18	2.46
Water container (lg)	429	0.115	0.08	0.20	0.88	0.30	1.28
Tire	311	0.084	0.06	0.15	0.67	0.22	0.98
Flower pot	223	0.060	0.04	0.11	0.52	0.15	0.77
Trash can	223	0.060	0.04	0.11	0.42	0.15	0.61
Bucket	174	0.047	0.03	0.08	0.31	0.12	0.46
Bird water (sm)	144	0.039	0.03	0.07	0.23	0.10	0.34
Tin can	130	0.035	0.02	0.06	0.16	0.09	0.24
Fish pond	86	0.023	0.02	0.04	0.10	0.06	0.15
Clay water container	65	0.017	0.01	0.03	0.06	0.05	0.09
Misc. container	59	0.016	0.01	0.03	0.03	0.04	0.04

Figures

Figure 1.

Plot of 30- and 60-day rainfall accumulations before surveys and the average of daily average temperature (°C) in Yogyakarta, Indonesia. Approximate dates of surveys are indicated by vertical, downward-pointing arrows. Total precipitation during the 2 months prior to each survey and the average temperature during survey are presented in Table1.

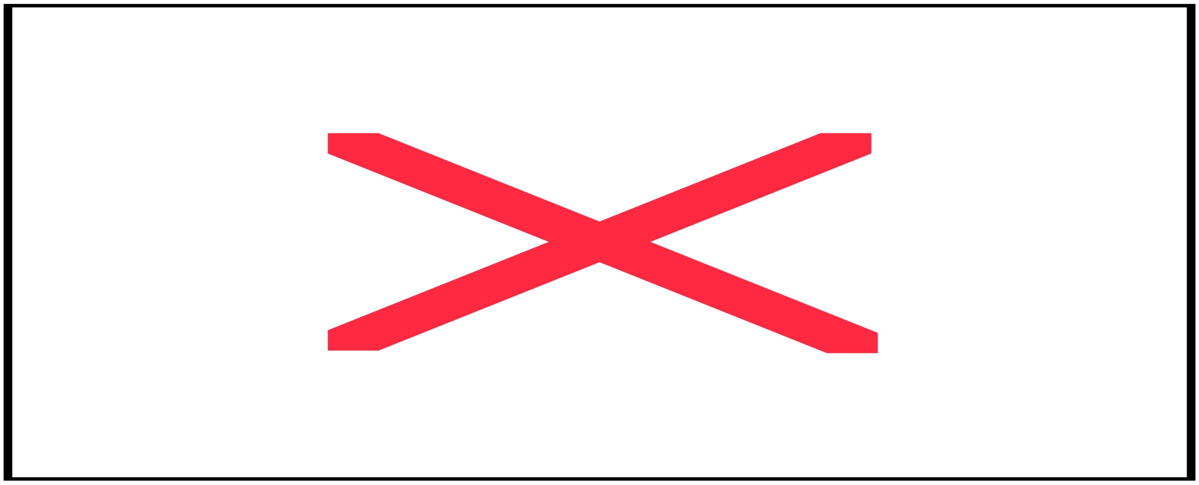


Figure 2.

Average number of potentially infectious replete feeds per newly-emerged female as a function of temperature and daily survival probability. This figure makes, for the purpose of comparisons, the unrealistic assumption that all mosquitoes take an infectious blood at one day of age. The actual number of potentially infectious bites per replete feed is unknown and may be as high 2 or 3 or more interrupted feeding attempts with resumption on the same or different host.[6]

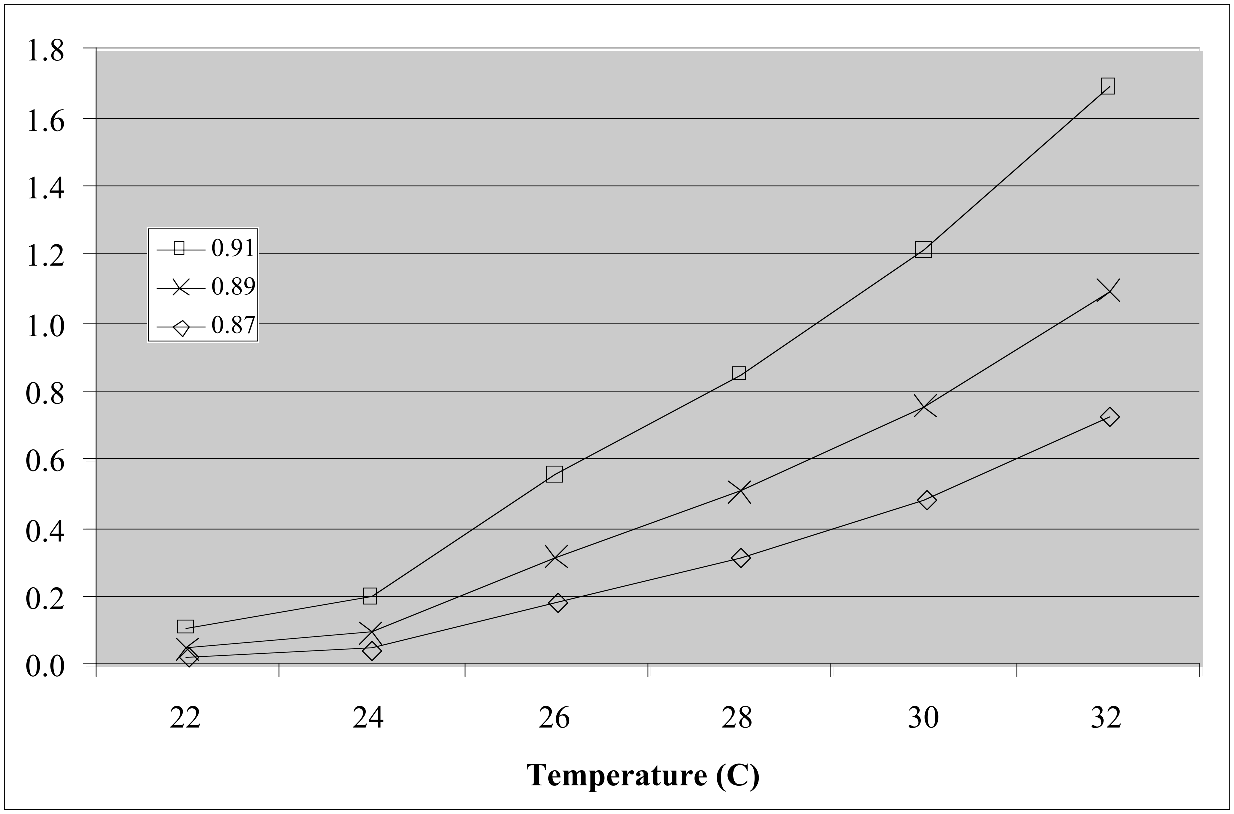
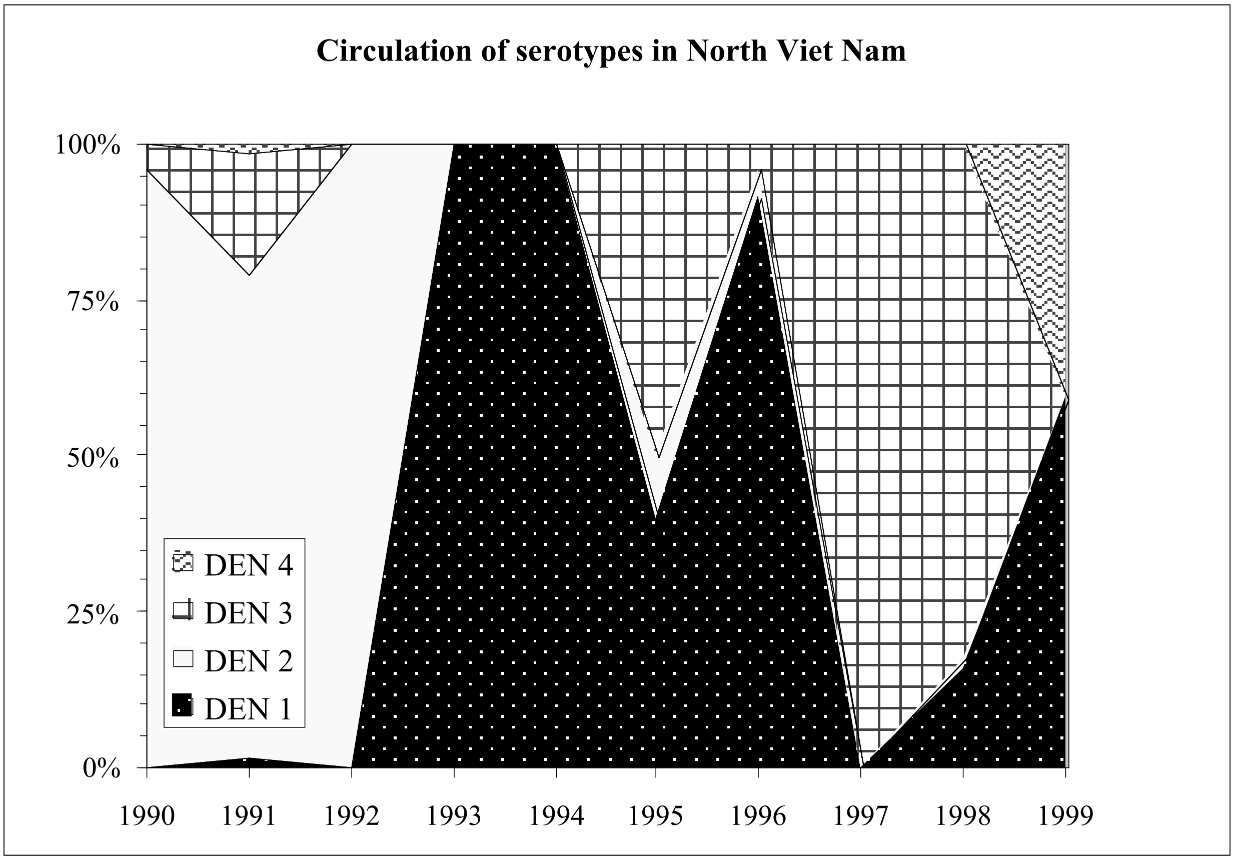
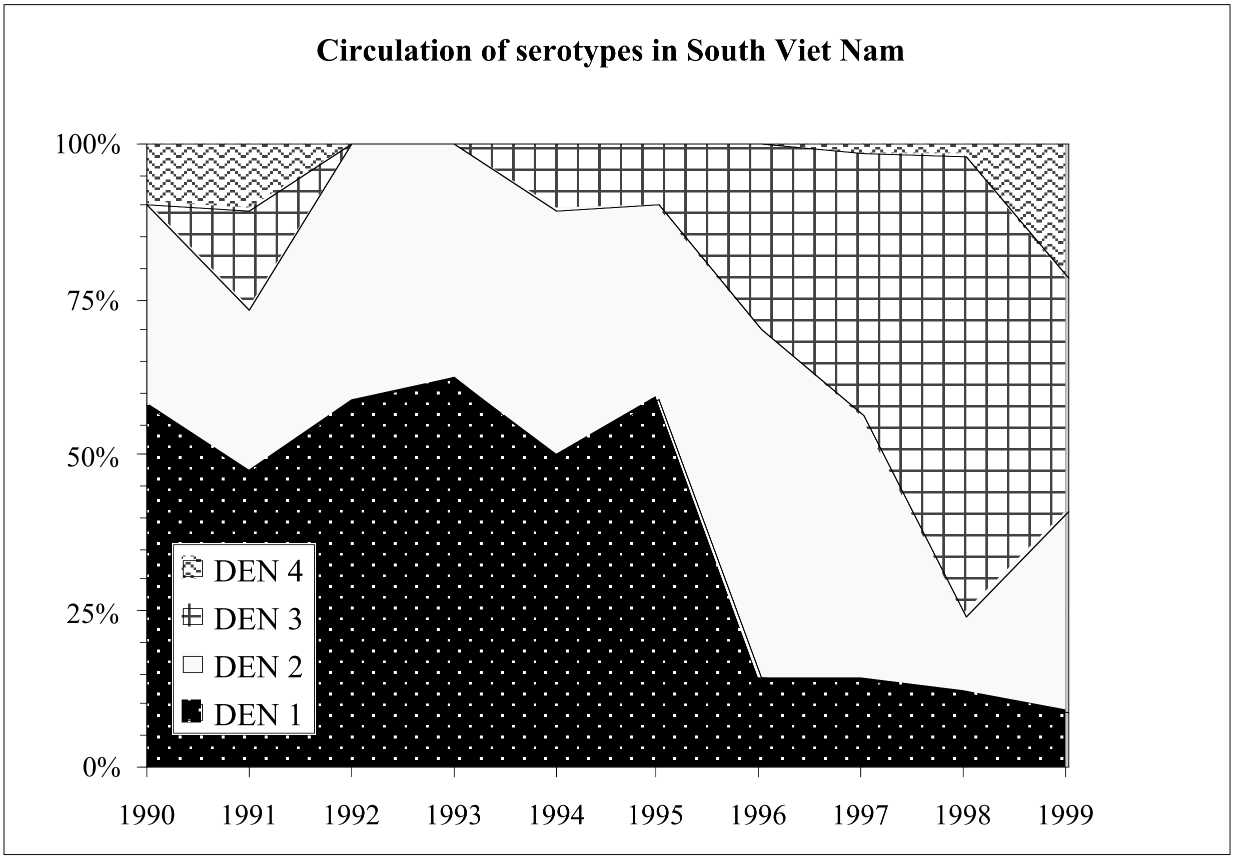


Figure 3.



Circulation of dengue serotypes in North Viet Nam between 1990 and 1999 based on virus isolation from febrile patients.

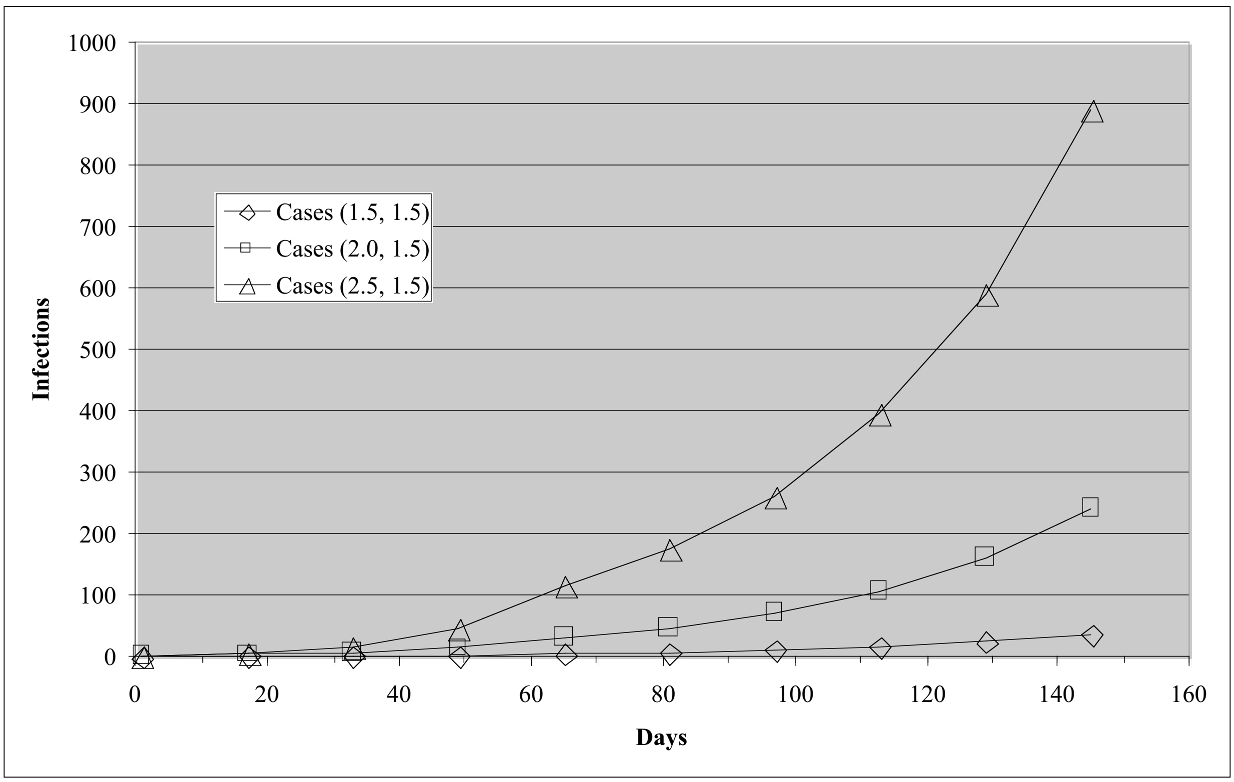
Figure 4.



Circulation of dengue serotypes in South Viet Nam between 1990 and 1999 based on virus isolation from febrile patients.

Figure 5.

Projected numbers of cases over time as a function of R_o. For illustration, we assume the periods of time between the onset in viremia in the first and subsequent infection cycles are multiples of 17 days. In each example, the epidemic is initiated with a single viremic individual. During the first 4 cycles, the pre-epidemic period (up through day 81), R_o is set to a constant value of 1.5, 2.0, or 2.5 for lines labeled *Cases (1.5, 1.5)*, *Cases (2.0, 1.5)*, and *Cases (2.5, 1.5)*, respectively. For cycles 5 through 10, R_o is set to a constant 1.5 in each case. The purpose of this illustration is to demonstrate that conditions several months before the appearance of large numbers of cases, the epidemic, significantly affect the magnitude of the event. Note in each example that the ratio of new cases in each cycle after day 81 is the same, 1.5, but the *absolute* numbers of cases after additional cycles in the epidemic phase is larger as a function of the number of infected in the pre-epidemic period. This then is the mechanism whereby environmental conditions that promote at the time an increased intensity of transmission but before there are large numbers of cases can become manifest months later as an epidemic under conditions that are less conducive to transmission.



List of Pre-prints and Publications Arising from this Grant

1. Focks, Dana A. March 2000. Dengue Risk Assessment and Control and the Role of Climate. *In* Proceedings of the Third NOAA Climate Workshop—Dominican Republic. See file "Abstract- Logistic reg EWS Yog & Bangkok.doc"
2. Focks, Dana A. 2001. "ENSO-based early warning system for dengue based on transmission thresholds. Mission report to the Regional Office of the Western Pacific. See files "MISSION REPORT.doc." and " Recommendations for control and surveillance.ppt." Funding by WHO.
3. Focks, Dana A., Lele, Subhash, *et al.* 2002. "Early warning systems for dengue in Indonesia and Thailand." Proceedings of BTR 2002. Unified Science & Technology for Reducing Biological Threats & Countering Terrorism. 14–15, March 2002. The University of New Mexico.
4. Focks, Dana A. 2003. "Epidemiology—Chapter 3" in Dengue. Scott B. Halstead, editor. Tropical Medicine–Science & Practice Series. Series editors: Geoffrey Pasvol & Stephen Hoffman. Imperial College Press. See file: "Focks Chapter 3 Epidemiology, ver 08.doc." *in press.*
5. Focks, Dana A. 2003. "A Review of Entomological Sampling Methods and Indicators for Dengue Vectors." TDR/WHO. See file: "Entomological Sampling Methods and Indicators for Dengue Vectors - TDR final edited version.doc." *In press.* See also WHO/TDR. Web site: http://www.who.int/tdr/publications/publications/pdf/dengue_review.pdf.
6. Focks, Dana A., Lele, Subhash, Haines, Christina, Juffrie, Mohammed. 2004. "Early Warning System for Dengue in Java, Indonesia based on Sea Surface Temperature Anomalies and Lagged Cases." Work completed, MS in preparation. See file "EWS Java ver 01.doc."
7. Focks, Dana A., Bangs Mike J, Juffrie, Mohammed, Nalim, Sustriayu, and Swerdlow, Joel L. A Dengue Control Strategy Based on Transmission Thresholds and Pupal/Demographic Surveys in Yogyakarta, Indonesia Quantifying Epidemiologically Significant Types of Breeding Containers. *Bull. Wld Hlth Org.* Work completed, MS in preparation. See file "Yogya surveys & strategy ver 04.doc."

List of Conferences and Workshops

1. Third NOAA Climate Workshop—Dominican Republic. NOAA-OGP funding. March 2000.
2. "Focus on Dengue." Workshop on Climate Variability and Climate and Their Health Effects in Pacific Island Countries. Apia, Samoa. 25-28 July 2000 NOAA-OGP and WHO funding.
3. "Early Warning System For Dengue In Indonesia And Thailand." Symposium on Integrated Methodologies for Infectious Disease: Prediction, Prevention, and Control. Presented at the annual meeting of the American Society of Tropical Medicine and Hygiene. 2001. See file "Integrated methods for ID prediction, control, preparedness DAFocks v 02.ppt."
4. "Modeling of Dengue Transmission." Singapore-WHO Health Forum—Environmental Dimensions and Policies for Dengue Prevention and Control. Singapore. October 2001. Funding by WHO.
5. "Dengue Control Modeling: Pupal Survey, Transmission Thresholds, and Targeted Source Reduction." International Conference on Dengue and DHF. November 20-24, 2000 Chiang Mai, Thailand. Funding from WHO.
6. "Models—Process Based, Transmission thresholds, Targeted Source Reduction, and ENSO-Based Early Warning System." Geographical Information Science in Studies of Vector-borne Diseases. Airlie, VA May 22-24, 2001. NOAA-OGP funding.
7. "Incorporating Climate Information Into Vector Control Models." Climate and Vector Control Workshop. Sponsored by NOAA's Office of Global Programs. Monday June 18, 2001. Crystal City, VA. NOAA-OGP funding.
8. "Early Warning Systems for Dengue in Indonesia and Thailand." BTR 2002. Unified Science & Technology for Reducing Biological Threats & Countering Terrorism. 14–15, March 2002. The University of New Mexico. See "BTR 2002 DAFocks 03.ppt."
9. "Impact of Anticipated Climate Change on Dengue in the Caribbean." Conference on Climate Variability and Change and their Health Effects in the Caribbean: Information for Climate Variability and Change Adaptation Planning in the Health Sector. Bridgetown, Barbados, May 20-21, 2002. NOAA-OGP and WHO/PAHO funding.
10. Tropical Disease Research/WHO. Multi-country validation study of *Aedes aegypti* pupal productivity survey methodology. Geneva, Switzerland. June 2003. Funding by WHO.
11. Tropical Disease Research/WHO. Multi-country validation study of *Aedes aegypti* pupal productivity survey methodology. Establishing the Protocols. San Juan, PR. September 2003. Support by WHO and US CDC.

Information Sheet [c]

Title: Dengue & El Niño-Southern Oscillation Events in Yogyakarta, Indonesia: Historical Correlations, Mechanisms, and Recommendations for Control Using Source Reduction.

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3. Pulsed Power and Laser Initiatives, Human Factors/Aerospace Medicine, Sandia National Labs
4. International Research Institute for Climate Prediction, Colombia University
5. The Tahija Foundation, Jakarta, Indonesia

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1. Focks, Dana A. March 2000. Dengue Risk Assessment and Control and the Role of Climate. *In* Proceedings of the Third NOAA Climate Workshop—Dominican Republic. See file “Abstract- Logistic reg EWS Yog & Bangkok.doc”
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4. Focks, Dana A. 2003. “Epidemiology—Chapter 3” in Dengue. Scott B. Halstead, editor. Tropical Medicine–Science & Practice Series. Series editors: Geoffrey Pasvol &

[c] Updated October 14, 2003

Stephen Hoffman. Imperial College Press. See file: “Focks Chapter 3 Epidemiology, ver 08.doc.” *in press.*

5. Focks, Dana A. 2003. “A Review of Entomological Sampling Methods and Indicators for Dengue Vectors.” TDR/WHO. See file: “Entomological Sampling Methods and Indicators for Dengue Vectors - TDR final edited version.doc.” *In press.*
6. Focks, Dana A., Lele, Subhash, Haines, Christina, Juffrie, Mohammed. 2004. “Early Warning System for Dengue in Java, Indonesia based on Sea Surface Temperature Anomalies and Lagged Cases.” Work completed, MS in preparation. See file “EWS Java ver 01.doc.”

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1. “Dengue Risk Assessment and Control and the Role of Climate.” Proceeding of the Third NOAA Climate Workshop—Dominican Republic. NOAA-OGP funding. March 2000.
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4. “Modeling of Dengue Transmission.” Singapore-WHO Health Forum—Environmental Dimensions and Policies for Dengue Prevention and Control. Singapore. October 2001. Funding by WHO.
5. “Dengue Control Modeling: Pupal Survey, Transmission Thresholds, and Targeted Source Reduction.” International Conference on Dengue and DHF. November 20-24, 2000 Chiang Mai, Thailand. Funding from WHO.
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10. Tropical Disease Research/WHO. Multi-country validation study of *Aedes aegypti* pupal productivity survey methodology. Introduced notion of early warning systems and targeted source reduction for control of dengue for Proof-of-Principal Committee, TDR/WHO. Geneva, Switzerland. June 2003. Funding by WHO. See file: "Entomological Sampling Methods and Indicators for Dengue Vectors - TDR final edited version.doc."
11. Tropical Disease Research/WHO. Multi-country validation study of *Aedes aegypti* pupal productivity survey methodology. Chaired workgroup on establishing protocols to test targeted source reduction concept. San Juan, PR. September 2003. Funding by WHO and US CDC.

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